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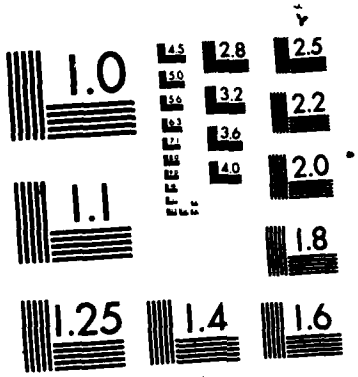

INSTITUTE REPORT NO. 235

EFFECTS OF ACUTE ACETYLCHOLINESTERASE INHIBITION BY PYRIDOSTIGMINE BROMIDE INJECTION IN EUVOLEMIC AND HYPOVOLEMIC CONSCIOUS SWINE

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Effects of acute acetylcholinesterase inhibition by pyridostigmine bromide injection in euvolemic and hypovolemic conscious swine--Wade et al

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

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The effects of acute reduction of blood cholinesterase activity, induced by pyridostigmine bromide injection (300 ug/kg intra-arterially), on physiological and biochemical parameters were assessed in conscious swine with and without hemorrhagic hypotension. Pyridostigmine administration reduced red blood cell acetylcholinesterase (AChE) activity by 61% with values returning to basal values within 3 hrs in both euvolemic and hypotensive animals. In hypovolemic animals plasma AChE activity was reduced by 35% compared to 14% in euvolemic animals. The greater reduction with hypovolemia was due to a 14% decrease during hemorrhage. The acute reduction of AChE activity by pyridostigmine injection in euvolemic and hypovolemic conscious swine did not significantly alter a range of biochemical and physiological parameters. Acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.

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Abstract

The effects of acute reduction of blood cholinesterase activity, induced by pyridostigmine bromide injection ~~(300 µg/kg intra-arterially)~~, on physiological and biochemical parameters were assessed in conscious swine with and without hemorrhagic hypotension. Pyridostigmine administration reduced red blood cell acetylcholinesterase (AChE) activity by 61% with values returning to basal values within 3 hrs in both euvolemic and hypovolemic animals. In hypovolemic animals plasma AChE activity was reduced by 35% compared to 14% in euvolemic animals. The greater reduction with hypovolemia was due to a 14% decrease during hemorrhage. The acute reduction of AChE activity by pyridostigmine injection in euvolemic and hypovolemic conscious swine did not significantly alter a range of biochemical and physiological parameters. Acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.

A-1

On the conventional battlefield many injuries result in hemorrhage (1). An injury caused by conventional weapons plus chemical agents resulting in hemorrhage will probably expose military personnel to chemical agents due to perforation of protective clothing by the missile producing the injury.

Trauma, such as burns and hemorrhagic hypotension, has been shown to reduce blood cholinesterase activity (2-5). These types of injury also may potentiate the actions of cholinergic drugs (6-8). Piscevic et al (9) found that simultaneous hemorrhage and chemical trauma resulted in the death of animals exposed to normally nonlethal doses of the nerve agent sarin. Hemorrhagic hypotension causes a reduction in blood cholinesterase activity, which may potentiate the lethal effects of nerve agents. Thus, the reduction in blood cholinesterase activity incurred during trauma on the battlefield may lead to an increased susceptibility to poisoning by nerve agents. We therefore investigated the physiological and biochemical effects of acute reduction of blood cholinesterase activity induced by pyridostigmine bromide administration in conscious swine with and without hemorrhagic hypotension.

Methods

Immature (2- to 3-month-old) Duroc swine (both gilts and barrows) were studied. The animals were purchased from a commercial supplier and housed in the Institute for at least ten days prior to surgery. They were fed a commercial ration (Purina, St Louis, MO) and allowed water *ad lib*.

After fasting overnight the animals were given a preanesthetic intramuscular injection of 0.08 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was induced using a face mask and maintained with an endotracheal tube. The posterior aorta was catheterized using sterile procedures (10). The catheter was tunneled under the skin and exited on the dorsal surface of the neck. The animals were observed until fully recovered and returned to holding cages. Catheter patency was maintained by flushing at 3- to 4-day intervals with heparin (1000 u/ml) in normal saline.

After 5 to 7 days of postoperative recovery each animal was fasted overnight. The following morning the animals were transported to the laboratory in a portable holding cage, and they remained in the holding cage. The animals were then connected to a 12-inch pressure-monitoring injection line that had been fitted with a three-way stopcock and filled with heparinized saline. The system was then flushed with heparinized saline and connected to a pressure transducer and monitoring system (Gould, 22405). Following a 30 minute equilibration period, the animals were hemorrhaged at 36 ml/kg, 50% of the estimated blood volume, in a logarithmic fashion (11, 12). Between minutes 0 and 60, equal increments of blood were withdrawn at 9, 19, 44, and 60 min. Upon completion of the hemorrhage the animals received an intra-arterial injection of normal saline (0.1 ml/kg, 0.9% NaCl), n=6 [data from these animals have been reported previously (12)] or pyridostigmine bromide (300 µg/kg, Mestinon® 5 mg/ml, Roche Laboratories, Nutley, NJ) n=7. Additionally, nine (n=9) animals which did not undergo hemorrhage were treated with the same dose of pyridostigmine bromide.

Measurements of hemodynamic variables were obtained at 0, 60, 62, 65, 75, 90, 105, 120, 135, 150, 165, 180, 210, and 240 minutes. Arterial blood samples were taken at 0, 60, 62, 65, 75, 90, 105, 120, 180, and 240 minutes. Additional blood samples were obtained during hemorrhage to determine acetylcholinesterase activity (see Fig. 1). Blood pressure, heart rate, and pulse pressure were measured for one minute prior to each sampling period and an average obtained. Plasma lactate (Sigma Chemical Co., St Louis, MO) and glucose (Beckman Instruments, Anaheim, CA) levels were measured by standard assay techniques. Hematocrit was measured by the microcapillary method. Blood gases were measured by a System 1303, (Instrumentation Laboratory, Lexington, MA). Acetylcholinesterase activities of the plasma and red blood cells were determined with a Technicon Auto Analyzer II system using a modification of the method of Ellman et al (13) adapted by Levine et al (14). Acetylthiocholine was used as the substrate (see Letterman Army Institute of Research Standard Operating Procedure OP-ACH-38, Auto Analyzer II Acetylcholinesterase Assay, 1982).

Data were analyzed using a two-way analysis of variance with comparisons made between groups and over time. Differences between means were assessed using the Newman-Keuls procedure. A significance level of 0.05 was

used on all tests. Values in the text are mean plus or minus the standard error of the mean.

Results

Hemodynamic: Heart rate was not altered during the sampling periods by hemorrhage or the administration of pyridostigmine (Table I). In euvolemic animals blood pressure was not altered by pyridostigmine; however, pulse pressure was significantly decreased by 12 mmHg. Blood pressure was reduced by hemorrhage and was not affected by injection of pyridostigmine.

Arterial Blood Gases: Arterial blood measurements were not altered in euvolemic animals by the injection of pyridostigmine (Table II). There were differences in arterial O_2 pressure and HCO_3 between the two groups of hemorrhaged animals, but these differences were not altered by pyridostigmine administration because a time group interaction was not noted. Thus, pyridostigmine did not change arterial blood gas in euvolemic and hemorrhaged animals.

Lactate/Glucose/Hematocrit: Although blood lactate and glucose levels increased during hemorrhage and hematocrit decreased, no effect from pyridostigmine administration was noted (Table III). Also in euvolemic animals no changes were noted due to this drug dosage.

Acetylcholinesterase Activity: Administration of pyridostigmine caused an immediate reduction in plasma and red blood cell AChE activity in both euvolemic and hemorrhaged animals (Table IV). Red blood cell AChE activity was acutely reduced (more than 50%) and gradually returned to basal levels over the following three hours (Fig. 1). In euvolemic animals given pyridostigmine, a 14% decrease in plasma AChE activity occurred, while in hemorrhaged animals a 35% reduction was noted. This difference was due to a 15% decrement in activity incurred over the course of hemorrhage.

Adverse Effects: Although few of the biochemical and physiological measurements were altered by pyridostigmine administration, side effects were noted. The side effects of pyridostigmine occurred only in the hemorrhaged animals. Upon administration of pyridostigmine following hemorrhage, a pronounced bradycardia was observed in 4 of 7 animals (Fig. 2). This bradycardia was rectified within

two minutes as there was no difference in heart rate or that of hemorrhage-control animals. In two animals hemorrhaged and given pyridostigmine, fasciculation was observed, and in one of these animals a period of labored breathing was noted. No adverse effects were noted in euvolemic animals treated with pyridostigmine.

Discussion

Pyridostigmine is a reversible inhibitor of acetylcholinesterase (AChE), the enzyme that degrades the neurotransmitter acetylcholine. In the present study pyridostigmine was used to evaluate the effects of acute reductions of AChE activity in hemorrhaged swine. Hemorrhage and trauma reduce AChE activity (2-5), which may be detrimental to individuals exposed to further reductions in activity, thus potentiating the actions of acetylcholine. In the present study the biochemical and physiological effects of further reductions in AChE activity following hemorrhage were investigated and no pronounced decrements noted. Furthermore, in euvolemic animals the reduction of AChE activity showed no effect.

The absence of changes in cardiovascular and biochemical parameters in the presence of reductions of 33% in plasma and 61% in red blood cell AChE activity may be due to the preponderance of AChE in tissues. In fact, a reduction of over 90% in blood activity is often required to elicit symptoms of acetylcholinesterase poisoning (15, 16).

Symptoms of acetylcholine toxicity (bradycardia, fasciculation, labored breathing) were noted in hemorrhaged animals following reduction of AChE activity induced by pyridostigmine administration. Though the symptoms were acute and inconsistent in this group, they are pronounced in that no adverse responses were noted in either of the other treatment groups, hemorrhage untreated or euvolemia with pyridostigmine. The presence of symptoms following pyridostigmine administration to hypotensive animals in the present study are in conflict with the observations of Piscevic et al (9). In their studies simultaneous hemorrhage and reduction of AChE activity by administration of a nonlethal dose of the nerve agent sarin to rats resulted in death with symptoms not observed or of "insignificant" intensity. Although symptoms were noted in the present study of swine, all animals survived the procedure, and the reduction in AChE

activity by pyridostigmine administration was probably not as pronounced as that induced by sarin.

In conclusion, acute reduction of AChE activity by pyridostigmine administration in euvolemic or hemorrhagic conscious swine failed to significantly alter a range of biochemical and physiological parameters. However, acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.

Recommendations

1. Further work is required to study the combined effects of trauma and exposure to nerve agents.

2. Future work should be conducted in an animal model that allows symptomatology as well as physiological and biochemical parameters to be assessed.

References

1. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. Milit Med 1984;149:55-62.

2. Assur MV, Ermakov AM. A change of blood cholinesterase activity in acute blood loss. Patol Fiziol Eksp Ter 1968;12:16-18.

3. Frawley JP, Artz CP, Howard JM. A study of plasma and erythrocyte cholinesterase activity in combat casualties. In: Howard JM ed. The systemic response to injury; vol 1. Washington, DC: Walter Reed Army Medical Center, 1956:261-267.

4. Viby-Mogensen J, Hanel HK, Hansen E, Sorensen B, Grace J. Serum cholinesterase activity in burned patients. I: Biochemical findings. Acta Anaesthesiol Scand 1975;19:159-168.

5. Wade CE, Waring PP, Gildengorin VL, Trail DS, Williams BF, Bonner GD, DeJong RH. Acetylcholinesterase activity of plasma and erythrocytes during hemorrhage in conscious swine. Presidio of San Francisco, California: Letterman Army Institute of Research (in press).

6. Whittaker M. Plasma cholinesterase variants on the anaesthetist. Anaesthesia 1980; 35:174-197.

7. Sunew KY, Hicks RG. Effects of neostigmine and pyridostigmine on duration of succinylcholine action and pseudocholinesterase activity. Anesthesiology 1978;49:188-191.

8. Viby-Mogensen J, Hanel HK, Hansen E, Grace J. Serum cholinesterase activity in burned patients. II: Anaesthesia, suxamethonium, and hyperkalaemia. Acta Anaesthesiol Scand 1975;19:169-179.

9. Piscevic S, Vojvodic V, Duknic M. Reciprocal effect of sarin and mechanical injury with loss of blood on survival of experimental animals. Vojnosanit Pregl 1972;29:155.

10. Traverso LW, Moores CC, Tillman FJ. A clinically applicable exsanguination shock model in swine. Circ Shock 1984;12:1-7.

11. Hannon JP, Jennings PB Jr, Dixon RS. Physiologic aspects of porcine hemorrhage. II: Alterations in heart rate and arterial pressure during fifty percent blood volume loss in the conscious animal. Presidio of San Francisco, California: Letterman Army Institute of Research, 1981; Institute Report No. 94.

12. Wade CE, Waring PP, Trail DS, Williams BF, Bonner GD, Gildengorin VL. Effects of atropine, 2-PAM, or pyridostigmine on responses to hemorrhage in conscious swine. Presidio of San Francisco, Letterman Army Institute of Research (in press).

13. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 1961;7:88-95.

14. Levine JB, Scheidt RA, Nelson JA. An automated micro-determination of serum cholinesterase. In: Skeggs LT, ed. Automation in analytical chemistry. Technician Symposia 1965. New York: Medical Inc., 1966:582-585.

15. Koelle GB. Neurohumoral transmission and the autonomic nervous system. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 5th ed. New York: MacMillan Publishing Co., 1976:404-444.

16. Koelle GB. Anticholinesterase agents. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 5th ed. New York: MacMillan Publishing Co., 1976:445-476.

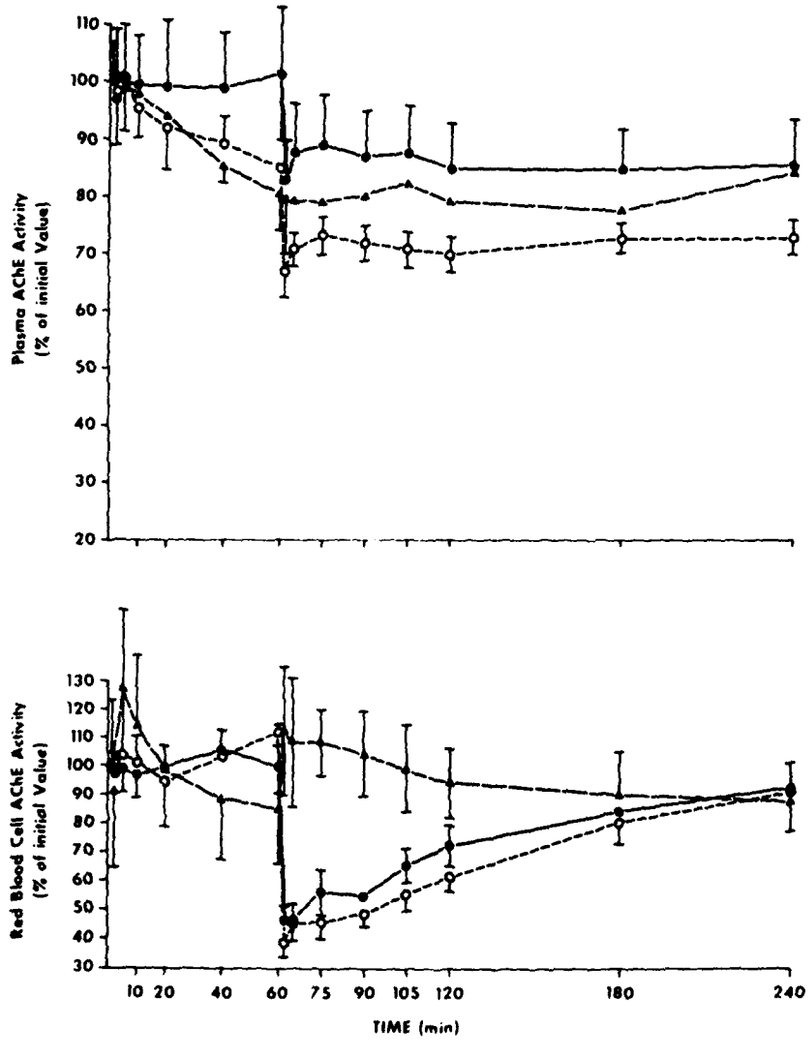

Fig 1: Red blood cell and plasma acetylcholinesterase activity (AChE), as a percent of initial activity, in hemorrhage-control (▲——▲), (for initial values, see Table IV), hemorrhage-pyridostigmine (O-----O), and control-pyridostigmine (●——●) conscious swine.

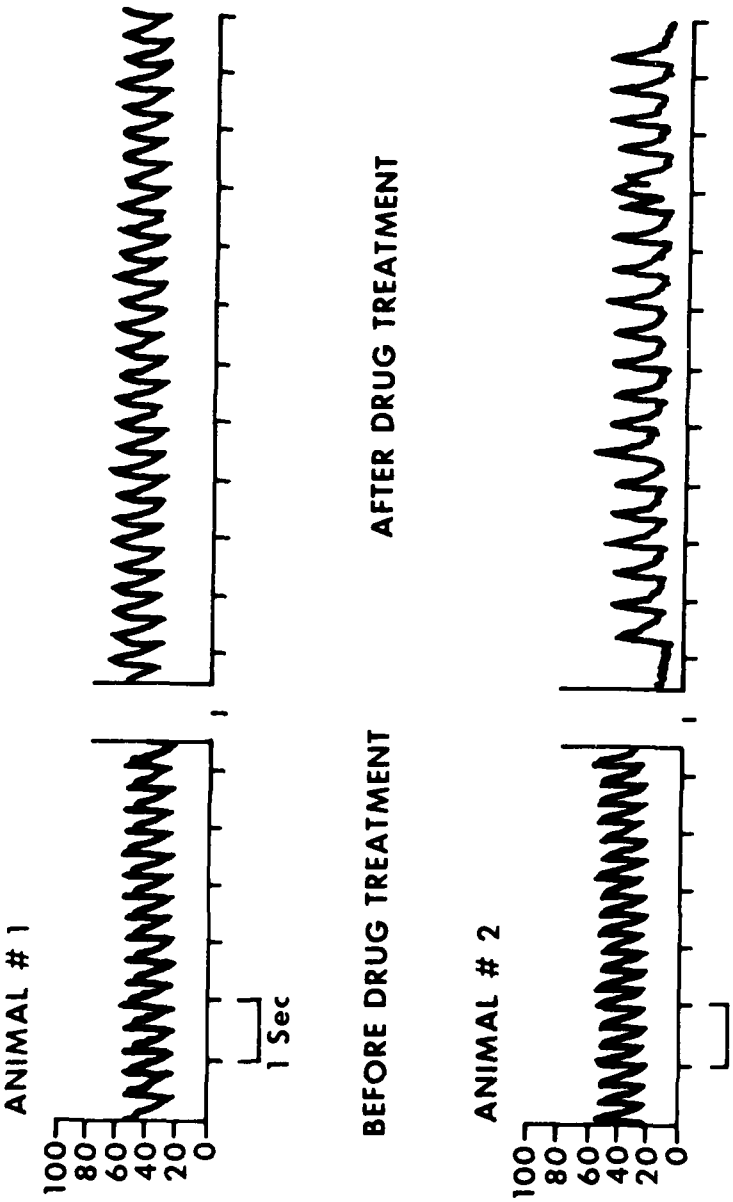

Fig 2: Blood pressure tracing in three animals prior to and immediately following intra-arterial injection of pyridostigmine (33 µg/kg).

Table I: Hemodynamic Responses

	Time (min)													
	0	60	62	65	75	90	105	120	135	150	165	180	210	240
Heart Rate (b/min)														
Hemorrhage-Saline	141±5	133±12	121±10	116±9	123±11	136±13	132±11	141±12	143±6	141±8	150±9	162±5	149±5	167±11
Hemorrhage-Pyrido	135±6	149±12	132±8	127±7	129±12	136±13	140±13	144±16	156±14	154±18	151±11	147±12	156±12	156±11
Control-Pyrido	130±5	133±9	130±8	127±6	131±6	127±6	125±4	127±4	131±4	129±5	135±6	137±6	133±4	129±5
Mean Arterial Pressure (mmHg)														
Hemorrhage-saline	96±5	38±3	39±4	48±6	45±5	41±2	50±4	44±4	50±5	52±2	62±8	49±4	57±5	56±4
Hemorrhage-pyrido	95±5	41±5	46±5	49±5	52±7	48±7	49±6	52±6	55±6	49±5	50±8	54±5	63±3	49±6
Control-pyrido	98±3	94±4	96±4	97±3	94±4	89±4	95±4	94±2	89±5	89±4	85±5	89±4	95±3	91±4
Pulse Pressure (mmHg)														
Hemorrhage-Saline	53±7	39±7	45±8	34±3	44±10	42±8	49±13	52±12	48±11	49±12	37±4	49±14	43±13	59±19
Hemorrhage-Pyrido	53±4	31±3	32±4	35±4	37±4	37±4	36±4	40±4	39±4	35±4	30±4	40±4	38±4	35±3
Control-Pyrido	56±2	53±3	53±3	58±3	57±4	54±4	52±4	53±4	45±4	46±4	42±4*	50±3	45±4	44±4

*: significantly different from the 60 min pre-injection value

Table II: Arterial Blood Gases

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
PO_2 (mmHg)										
Hemorrhage-Control	99±3	124±5	115±5	114±3	112±5	107±9	117±6	108±6	109±6	121±8
Hemorrhage-Pyrido	85±3*	101±8*	91±7*	92±3*	92±4*	91±4*	89±4*	88±4*	96±4*	91±3*
Control-Pyrido	92±3	93±3	89±3	90±3	86±4	87±2	91±2	89±3	87±3	94±3
PCO_2 (mmHg)										
Hemorrhage-Control	37±1	28±2	31±2	30±2	31±1	32±1	33±2	36±1	35±1	32±1
Hemorrhage-Pyrido	38±1	31±1	34±3	33±1	32±1	32±1	32±1	35±1	35±2	35±1
Control-Pyrido	40±1	38±1	39±1	39±1	40±1	39±1	38±1	39±1	40±1	38±1
HCO_3										
Hemorrhage-Control	25±1	20±1	21±1	20±1	20±1	21±1	22±1	23±1	24±1	24±1
Hemorrhage-Pyrido	27±1*	25±1*	24±1*	23±2*	23±2*	23±1*	23±1*	25±1*	26±1*	26±1*
Control-Pyrido	28±2	27±1	27±1	27±1	27±1	27±1	27±1	26±1	26±1	27±1
pH										
Hemorrhage-Control	7.43±0.01	7.46±0.02	7.42±0.02	7.42±0.01	7.41±0.01	7.42±0.01	7.43±0.01	7.43±0.01	7.42±0.02	7.48±0.02
Hemorrhage-Pyrido	7.50±0.01	7.50±0.02	7.47±0.03	7.45±0.03	7.45±0.03	7.45±0.03	7.47±0.03	7.45±0.03	7.46±0.03	7.47±0.02
Control-Pyrido	7.46±0.01	7.48±0.01	7.45±0.02	7.45±0.01	7.45±0.01	7.47±0.01	7.46±0.01	7.45±0.01	7.45±0.01	7.46±0.01

*: significantly different from hemorrhage-saline, P≤0.05.

Table III: Lactate/Glucose/Hematocrit

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
Lactate (mg/dl)										
Hemorrhage-Control	9±1	56±15	63±12	60±10	61±13	59±12	52±11	53±11	27±9	22±9
Hemorrhage-Pyrido	7±1	32±6	42±8	47±9	52±9	50±10	44±7	34±9	24±7	18±7
Control-Pyrido	6±1	8±2	8±2	8±1	6±1	5±1	6±1	6±1	6±1	5±1
Glucose (mg/dl)										
Hemorrhage-Control	89±7	145±24	157±16	163±29	162±19	150±20	138±21	151±21	129±18	123±10
Hemorrhage-Pyrido	107±17	126±8	155±17	169±26	177±22	150±18	153±13	136±13	144±17	130±15
Control-Pyrido	88±6	93±8	93±8	96±8	87±8	92±8	90±10	91±9	95±11	96±9
Hematocrit (%)										
Hemorrhage-Control	27±2	23±1	23±1	23±2	22±1	23±2	22±2	22±2	22±2	21±1
Hemorrhage-Pyrido	27±1	22±1	23±1	24±2	22±2	22±1	22±2	22±2	22±2	22±2
Control-Pyrido	26±1	25±1	26±1	26±1	26±1	26±1	25±1	25±1	25±1	25±1

Table IV: Acetylcholinesterase Activity

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
Plasma AChE (u/ml)										
Hemorrhage-Saline	0.50±0.01	0.40±0.02	0.40±0.02	0.30±0.02	0.30±0.02	0.40±0.02	0.41±0.02	0.30±0.02	0.30±0.03	0.42±0.02
Hemorrhage-Pyrido	0.41±0.02	0.36±0.01	0.27*±0.02	0.29*±0.01	0.30*±0.01	0.29*±0.01	0.29*±0.01	0.29*±0.01	0.30*±0.01	0.30*±0.01
Control-Pyrido	0.42±0.05	0.43±0.05	0.36°±0.03	0.37°±0.04	0.37°±0.04	0.37°±0.03	0.37°±0.03	0.36°±0.03	0.36°±0.03	0.36°±0.03
Red Blood Cell AChE (u/ml Pc)										
Hemorrhage-Saline	4.11±0.50	3.47±0.79	4.53±0.89	4.30±0.83	4.41±0.43	4.23±0.62	4.01±0.65	3.68±0.46	3.68±0.64	3.50±0.37
Hemorrhage-Pyrido	3.93±0.36	4.46±0.50	1.54*±0.16	1.89*±0.19	1.84*±0.18	1.91*±0.16	2.23*±0.20	2.41*±0.19	3.21±0.27	3.50±0.39
Control-Pyrido	4.81±0.39	4.82±0.36	2.14°±0.31	2.28°±0.33	2.73°±0.40	2.66°±0.38	3.15°±0.29	3.53°±0.32	4.12±0.33	4.41±0.32

*significantly different from hemorrhage-saline, P<0.05.

°significantly different from 60- min value in control-pyrido, P<0.05.

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